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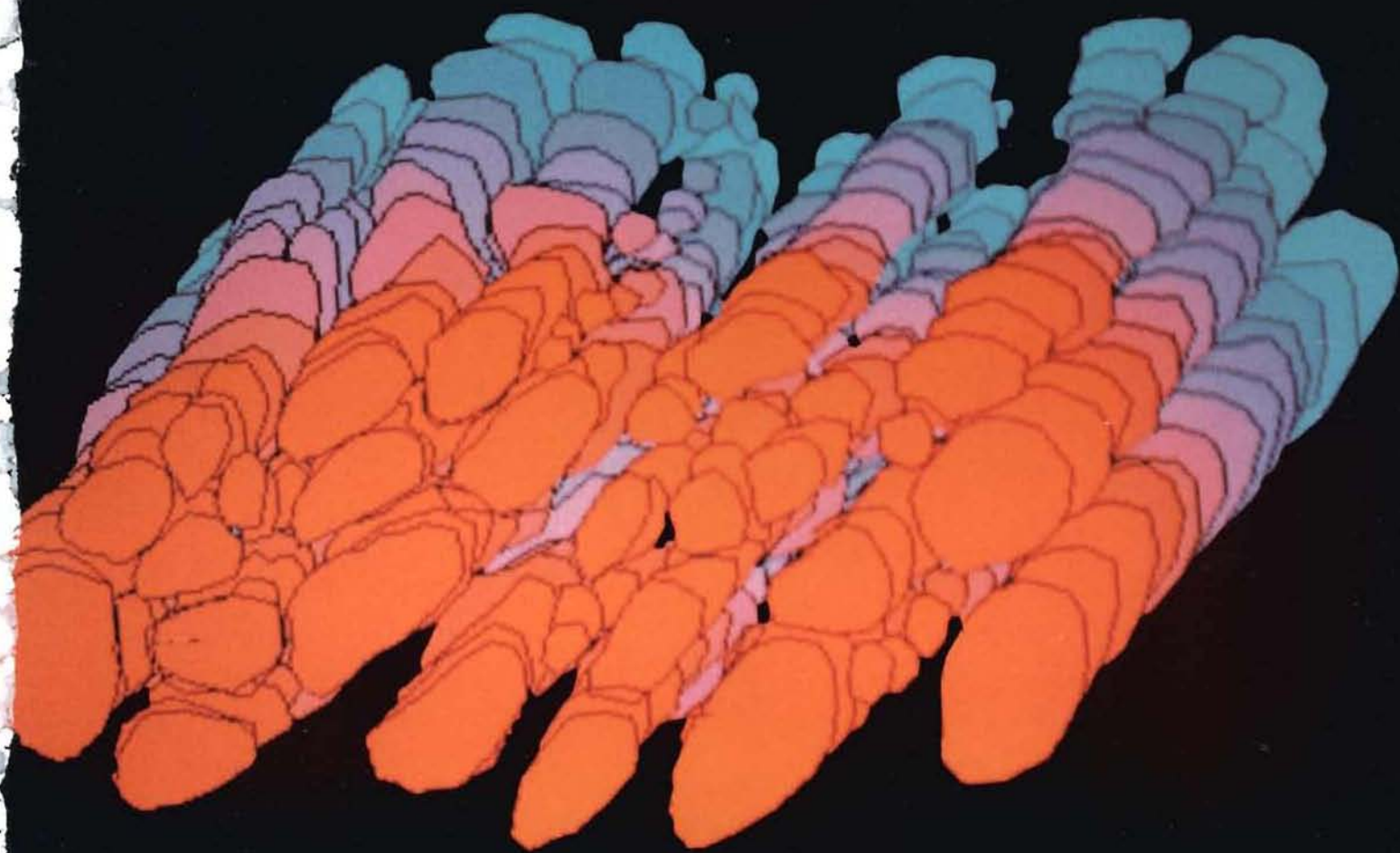
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WASHINGTON UNIVERSITY SCHOOL OF MEDICINE

FALL 1990

OUTLOOK



Making Connections



This year's Washington University Medical Center annual report focuses on genetics. Pictured here is an artist's rendering of deoxyribonucleic acid, or DNA, the "master molecule." Copies of the annual report are available by calling the Office of Medical Public Affairs at (314) 362-8258.

OUTLOOK

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**Executive Director,
Medical Public Affairs**

Don Clayton

Interim Editor

Karen Burns

Design

Jean Lopez

Photography

Tom Heine

Circulation

Randi Hantak

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School of Medicine

On the Cover:

School of Medicine researchers are developing a computer mapping process to help surgeons better mend severed nerves. This 3-D image assists in nerve fascicle alignment; incorrectly matched fascicles can grow improperly to impede restoration of function and sensory perception. See story on page 6.



Making Connections

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Washington University Selected As Federal Gene Research Center

The School of Medicine has been designated one of the Public Health Service's first four centers of investigation for the federally funded human genome initiative — a project with the goal of deciphering the complete genetic message of human beings at the molecular level. The designation brings with it a five-year grant with a first-year award of \$2.3 million from the National Institutes of Health to establish a new Human Genome Center at Washington University.

"This is wonderful recognition of the strengths this institution has amassed in the area of genetics research," says Chancellor William H. Danforth, M.D. "The diligence and creativity of our fine faculty have once again secured for us a key role in an important national research initiative."

The results of the highly competitive national selection process were announced in Washington D.C. by Secretary of Health and Human Services Louis Sullivan, M.D. Washington University and the other three recipients will receive a total of more than \$10 million this first year. The National Center for Human Genome Research, the component of NIH established to oversee its part of the Human Genome Project, is expected to make awards to additional institutions next year.

"It's a huge task, but it's more of an investment than an expense," says David Schlessinger, Ph.D., who will direct the new genome

center at Washington University. Schlessinger adds that when the genome is adequately mapped, "scientists can efficiently work out all of human biology at the molecular level. This is the best route to understanding

is proud to be among the institutions whose outstanding scientists will lead this national effort."

Among the biggest scientific undertakings in history, the Human Genome Project will decipher the genetic

chromosomes. A later goal is the exact sequencing of the molecular "base pairs" that constitute the chromosomes and provide a code for protein production.

The Washington University project has three parts, each based on the power of Yeast Artificial Chromosome (YAC) technology. YACs were developed in the Washington University laboratory of Maynard V. Olson, Ph.D., and have increased the capabilities of the molecular geneticist's lab by a full order of magnitude over conventional techniques. Through YAC technology, large portions of the human genome are introduced into yeast chromosomes that are adopted and then cloned by the plant. Because of their size, the clones can hold even large genes intact and can be overlapped to reconstruct maps of large parts of the human genome.

The St. Louis center aims to continue the development of technology for genome analysis while reaching its three goals. The first is to locate a number of genes of special medical or research interest in YACs. "For example," Schlessinger says, "we know that genes in a particular region of about 4 million base pairs are responsible for the rejection of transplanted tissues. Using YAC technology we have been locating and cloning these genes," in work led by David Chaplin, M.D., Ph.D.

The other two projects have as their goals detailed maps of two human chromo-



David Schlessinger, Ph.D. (left) and Maynard V. Olson, Ph.D.

most, if not all, of the 4,000 inherited diseases."

"This is a great opportunity; understanding the human genome will yield enormous benefits to mankind," says William A. Peck, M.D., vice chancellor for medical affairs and dean. "Washington University School of Medicine

messages locked away in each of the body's cells. The complete set of messages, or genome, is inscribed in the 100,000 or so genes on 23 pairs of chromosomes. One of the project's five-year goals is the development of maps showing the location of the genes on each of the

somes, those known as seven and X. The maps will establish "guideposts" in the expanse of DNA, making it easier for researchers to find their way to genes of interest. Leading the project with Schlessinger are co-principal investigators Helen Donis-Keller, Ph.D., and Philip P. Green, Ph.D., both experts on human genetics and gene-mapping, and Olson, the developer of YACs and associated technology.

Approximately 104 genes are already known to reside on chromosome 7, which is believed to contain a total of about 5,000 genes. Several of these, including the cystic fibrosis gene and those that control the immune response, are involved in disease. The role of the X chromosome in human disease has also made it the target of ardent study. Genes for hemophilia A and B, diseases of the adrenal gland, fragile X syndrome, and color blindness are located on the X chromosome.

The university's Center for Genetics in Medicine — already involved in organizing the world's first complete collection of YACs, screening them and sharing them with investigators elsewhere — was instrumental in bringing one of the genome initiative's first centers of investigation to Washington University, Schlessinger says. "We have a fully organized genetics research center here, with a sustained supply of resources, space and facilities developed by the School of Medicine, the McDonnell Foundation and the Biomedical Agreement with Monsanto, in conjunction with federal funding," he says. ■

Andersson Named Assistant Dean For Finance

George E. Andersson has been named assistant dean for finance.

The appointment, effective Oct. 1, was announced by William A. Peck, M.D., vice chancellor for medical affairs and dean. This is one of numerous appointments being made in an administrative reorganization at the School of Medicine.

"It's wonderful to have someone with his expertise and experience in an academic medical center to assist us in the management of our financial resources in an increasingly complex environment," Peck said.

Andersson comes to St. Louis from Georgetown University School of Medicine where he served as controller. In his new position, Andersson will organize and administer functions associated with the management of financial resources of the School of Medicine. He will be responsible for the central administrative budget, monitoring the financial performance of academic and non-academic departments and coordinating the preparation and presentation of financial reports for the medical school.

He also will be responsible for the administrative management of the medical school's finance office, including financial information systems and selected business and clinical support services. In addition, he will represent

the medical school in negotiations with third party payors, affiliated teaching hospitals and other organizations contracting for services.

Andersson has worked the last 13 years at Georgetown. He also has served as director of finance for the University of Kentucky School of Medicine and prior to that as assistant to the dean at Loma Linda University School of Medicine.

Andersson is an active member of the Medical Group Management Association and of the Association of American Medical Colleges in the groups on business affairs and institutional planning. He received a bachelor's degree in economics in 1971 from the University of California, Riverside. ■

Cured: MS-like Disease in Mice

The immune systems of adult humans make millions of antibodies, each one directed at a specific target. Capable of extreme discrimination, antibodies that bind to one protein may completely ignore another that differs in only a few amino acids, the building blocks of all proteins. Such precision makes antibodies valuable as tools for identifying small molecules and specific proteins.

Now, therapy with monoclonal antibodies has suppressed an autoimmune disease in mice, showing for the first time that such treatment

is feasible. The technique, devised by collaborators at Washington University School of Medicine and the California Institute of Technology, cured experimental allergic encephalomyelitis, or EAE, in mice, a widely used model for human multiple sclerosis (MS).

Researchers achieved dramatic reversal of paralysis by giving the antibodies to sick animals. They also prevented symptoms in 95 percent of the cases in which they injected the antibodies before administering the disease agent.

In both EAE and MS, T-

cells of the immune system that normally control disease by attacking foreign invaders inexplicably turn on the host and assail the protective sheathing around nerves. In humans, MS affects many parts of the central nervous system, causing paralysis, loss of coordination, blurred vision and other symptoms.

Immune system disorders like MS are especially troubling to physicians because the treatment can often be worse than the disease. Historically, treating autoimmune disorders has required suppressing the immune system almost entirely, leaving the body susceptible to serious infections of many types. The new work promises a

method for deactivating only the precise elements of the immune system that go wrong to cause a particular disease. "The rest of the body's defenses remain intact," explains Washington University's Osami Kanagawa, M.D., Ph.D., one of the researchers responsible for the advance.

When will the new technique be available to work in human autoimmune disorders such as MS, diabetes and rheumatoid arthritis?

Kanagawa, an associate professor of pathology and medicine, warns that it may take as long as 10 years, largely because the human immune system is so much more complicated than the mouse's. Commenting on the work, Charles Janeway, M.D., professor of immunobiology at Yale University School of Medicine, adds that the two systems — the mouse and the human — are, "genetically distinct. Antibodies that work in the mouse don't work in the human." Still, Janeway says, we should be "optimistic" about developments such as this one.

To create the multiple sclerosis-like illness in mice, the researchers used a technique developed in Leroy E. Hood's biology laboratory at Caltech. They injected mice with a protein based on myelin, the material that forms nerve sheaths. The material prompted an immune response not only to the foreign protein but also to the myelin of the mice's own nerve sheaths. "EAE is the result of T-cells attacking the nervous system," explains Kanagawa.

The investigators then assayed the T-cell popula-

tions of the affected mice and isolated those cell types that proliferated in response to the injection of the myelin-based protein. They learned that "four types of T-cells are involved in the response," says Kanagawa. "The types are based on how their receptors are configured."

Receptors, essential to a T-cell's work, are protein

the receptors of all four T-cells involved — the disease was suppressed and the sick mice got better. When antibodies to both V-beta elements involved were administered prior to the illness-inducing myelin-based protein, EAE was prevented.

Specifically, three of five mice suffering from EAE improved from hind-leg

long lasting. The researchers report that the culprit T-cells did not begin to reappear until 12 weeks after treatment with the combined antibody therapy.

The antibodies work by preventing the T-cell receptors from recognizing and binding to their targets, Kanagawa says. "Essentially, the antibody covers up the V-beta part of the receptor so that the T-cell can no longer 'see' the antigen it is trying to attack."

The experiments are the first in which the introduction of antibodies to T-cell receptors has suppressed an ongoing autoimmune disease. "The approach against T-cells by antibodies works," Kanagawa says. The results of the study were published recently in the *Journal of Experimental Medicine*.

Hood and Kanagawa have shown the technique to be effective in a mouse model; now, Kanagawa asks, in what human disorders will it work. He is currently exploring the possibility of applying it to autoimmune diabetes, developing antibodies to the immune system culprits involved. "But you can't make a human patient sick. Analyzing T-cell populations in people with a disease is much harder because the human genetic background is so complex."

Kanagawa hopes to make antibodies that will be effective in a large part of the population. "If a human autoimmune disease is the result of T-cells with just a few types of receptors, this new technique will work," he says. But if 20 or more different types are involved, the problem becomes unmanage-

"Analyzing T-cell populations in people with a disease is much harder because the human genetic background is so complex."

elements on the cell's surface. Each T-cell has a receptor designed to recognize a single intruder. A T-cell receptor is usually described as having two functional parts, referred to as its V-alpha and V-beta elements.

Two V-alpha and two V-beta elements were found to characterize the T-cells responsible for causing EAE, making four possible T-cell types. An antibody developed previously worked against one of the V-beta elements, eliminating two of the four possibilities. That left just two T-cell types to deactivate.

Kanagawa's lab created a monoclonal antibody to the remaining V-beta element. When the combined antibody therapy was administered to mice with EAE — disabling

paralysis to normal in two to seven days after injection with the antibodies. A fourth mouse improved significantly, with only tail paralysis remaining. The fifth animal, suffering whole body paralysis, died. In five control mice, the disease either stayed the same or worsened over two weeks of observation.

Treatment with the antibodies before EAE was induced produced equally promising results. In 19 of 20 mice that received the combined antibody therapy, EAE did not appear when the researchers tried to induce it. The 20th animal developed only mild paralysis. Fourteen of 17 control animals that got no antibodies developed EAE as expected.

Equally important is that the protection appears to be

able and, again, a large portion of the immune system must be disabled to treat the disorder.

In the mouse, approximately 25 types of the V-beta component of T-cell receptors are known, and antibodies to 10 of them have been developed. In humans, twice that number of V-beta elements may be involved in defining T-cell receptors, yet only four antibodies to them currently exist. Isolating the tiny protein packages that make up a portion of the receptor is part of the problem: The complete receptor accounts for less than a tenth of one percent of the protein on a T-cell's surface.

But once the V-beta component has been identified, Kanagawa says, making the antibody to it is a relatively straightforward process. The technique that continues to revolutionize medicine involves stimulating and harvesting the spleen cells that produce antibodies, fusing those cells to myeloma (tumor) cells to form "hybridomas," and finally growing the hybridomas in a culture to produce a supply of antibody to the agent initially used to stimulate the spleen cells.

One of Kanagawa's long-range goals is to make antibodies against all of the 50 V-beta elements of human T-cell receptors. "It may take four or five years," he predicts. But such an arsenal — its elements used alone and in combination — should prove effective against a wide range of human autoimmune diseases. Monoclonal antibodies will then establish for themselves an even larger role in medicine. ■

Ophthalmology Receives Grant For Eye Research

The Department of Ophthalmology and Visual Sciences has received an unrestricted grant of \$50,000 from Research to Prevent Blindness (RPB), a voluntary organization committed to the financial support of eye research.

The award was announced by Henry J. Kaplan, M.D., professor and head of the Department of Ophthalmology and Visual Sciences.

"The unrestricted grant is very important to us," says Kaplan, "because it allows the department flexibility to provide support where it is most needed." He notes that RPB is one of the few organizations that provides unrestricted funds.



Henry J. Kaplan, M.D.

Washington University has one of the world's largest research programs devoted to ophthalmology and visual science. The department is known for its expertise in retinal neurobiology, and in the past year has been ex-

panding the research faculty to develop centers of expertise in immunology and molecular biology. Research projects include studies of glaucoma, retinal degeneration, crossed-eyes in children, amblyopia (impaired vision without a detectable lesion or disease of the eye), retina transplantation, and the ocular manifestations of diabetes and other systemic diseases.

During the past 29 years, the ophthalmology department has received \$601,900 in RPB funds. RPB provides annual grants to 62 medical schools and is the world's leading voluntary organization in support of eye research. ■

Alzheimer's Center To Receive \$8.6 Million

The Alzheimer's Disease Research Center (ADRC) has been awarded \$8.6 million for the next five years from the National Institute on Aging (NIA).

The funding is a renewal of a \$3.75 million award that established the local ADRC in 1985. The NIA has funded 15 ADRCs nationwide to encourage research on the basic science, clinical and behavioral aspects of Alzheimer's Disease. Additionally, the centers train scientists and health care professionals, and inform the public about research advances.

Washington University's ADRC studies behavioral and biomedical aspects of healthy aging compared with that of Alzheimer-type dementia, examines the impact of Alzheimer's on the family and the community, seeks biological factors in the nervous system that could be associated with the disease, and explores changes in the aging brain that may contribute to Alzheimer's Disease.

The center's interdisciplinary approach allows established investigators from many departments to conduct a wide range of studies. Currently there are six multi-year projects and five pilot

studies, many of them related to biochemical changes in the brain. Previous projects have included epidemiologic studies to identify predictors of the disease and studies on community attitudes.

The ADRC is directed by Leonard Berg, M.D., professor of neurology and director of the School of Medicine's Memory and Aging Project. The Memory and Aging Project is a long-term study of intellectual function in people aged 65 and older. ■

Making Connections:

Using Computers to Map Nerve Pathways

by Kleila Carlson

Like an electrician who reconnects color-coded wires twisted inside a broken cable, the surgeon who mends a mangled arm must carefully match cut ends of minute nerve fibers that wend their way from the elbow to the hand.

The electrician's convenience of color-coding is not afforded to the physician, whose job it is to restore feeling and movement in the forearm, wrist and hand by

matching unmarked ends. But a new computer mapping process developed at Washington University School of Medicine in St. Louis may help surgeons better mend severed nerves and restore the precious sense of feeling and movement. Researchers predict that clinicians in the operating room soon will have access to a computer atlas on nerve repair as a result of efforts currently underway here.

The course nerve fibers travel has mystified scientists for years and confounded surgeons' attempts to reconstruct nerves damaged by injury or disease. The ability to precisely chart the braided path of these strands, which are called fascicles and are clustered in bundles just inside the nerve sheath, could significantly improve a patient's chances of complete recovery following micro-neurosurgery. Toward that end, researchers have spent more than two years developing techniques to define the pathways of these nerve bundles in the forearm and hand. Scientists have known for more

occur infrequently within centimeter distances — 75 percent of cross sections showed zero or one fascicular branch. In addition, they learned that fascicular branching is most likely to occur three to five centimeters below the wrist where the major motor branch separates from the median nerve to continue toward the hand with sensory and motor fibers.

Previous studies, which lacked the precision of the Washington University investigation, have shown a gnarled anatomy and offered little hope for successful repair over distances greater than three centimeters.

With the new information, researchers expect to mathematically predict the similarities that exist between like nerves of different people and develop a computer atlas that will serve as a reference for the surgeon in the operating room.

"The study results already are helpful as far as dissection and (internal) examination of the nerves are concerned," says Paul M. Weeks, M.D., professor of surgery and head of the division of plastic surgery. "We are grossly looking at the nerve and identifying fascicles from photographs of sections which have been prepared in the lab. Within two to three years, we will have compiled enough information to create a computer reference for clinicians."

Because injured nerve ends are often traumatized and tattered, damaged sections must be cut away so clean ends can be sutured. Realigning these unrelated sections is difficult — even over short distances of five to 10 millimeters only 50 percent of fascicles are properly identified by the unaided surgeon. If the nerve ends are not matched correctly, proper innervation to muscles and skin will not occur, and the patient's motor and sensory function may remain permanently impaired.

Watchmaker is one of the authors of the article "Fascicular Topography of the Median Nerve," that will appear in a forthcoming issue of *The Journal of Hand Surgery*. Co-authors on the study were Cesar Gumucio, M.D., and R. Evan Crandall, M.D., residents in the division of plastic surgery; Michael Vannier, M.D., professor of radiology, Mallinckrodt Institute of Radiology; and Paul M. Weeks, M.D., head of the division of plastic and reconstructive surgery. The research team received the Emanuel Kaplan Award at the American Society for Surgery of the Hand Meeting in 1988 for an earlier phase of its studies.

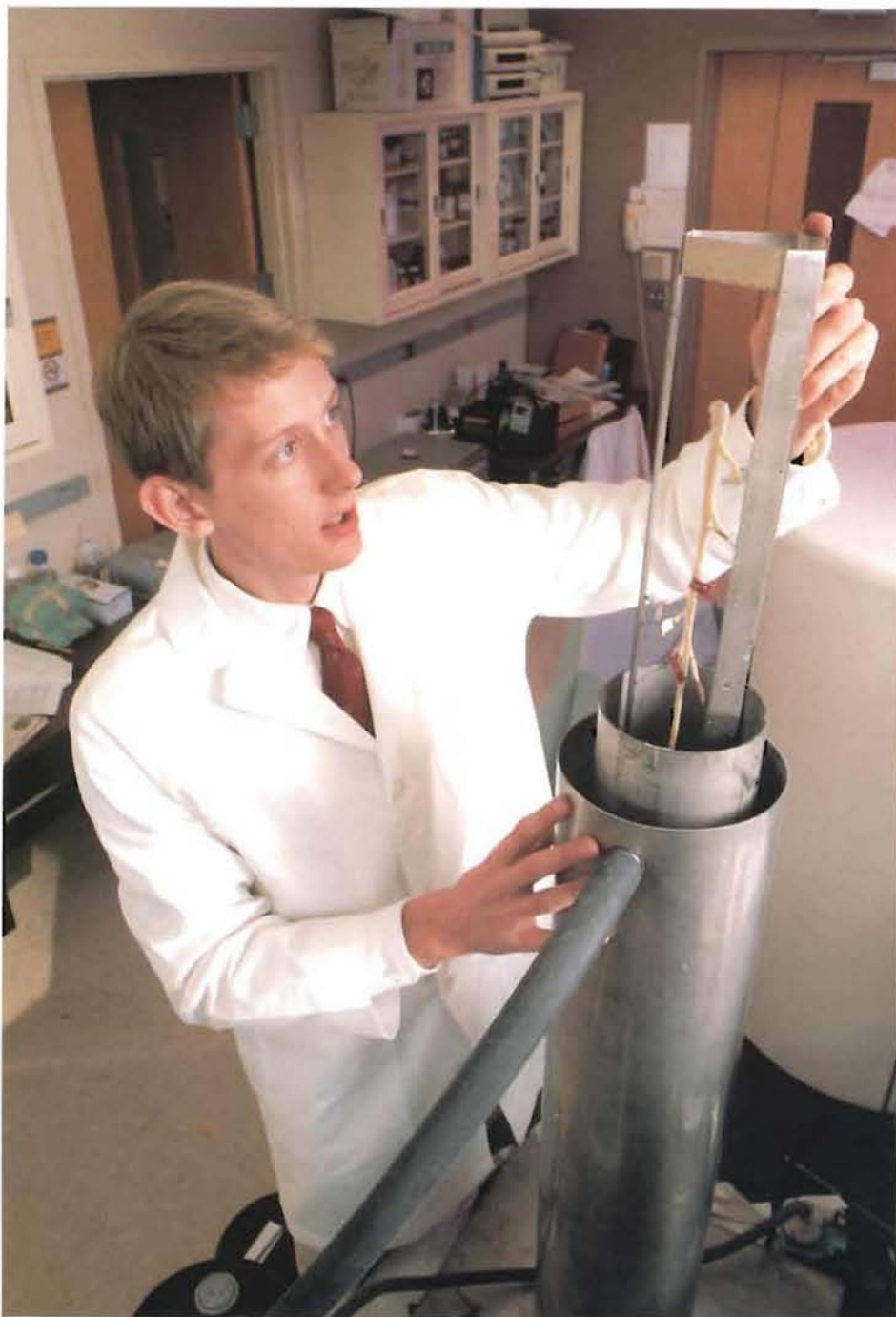


Greg Watchmaker, M.D., left, and Herluf Lund, M.D., prepare a nerve specimen for study.

than 40 years that the cross-sectional arrangement of nerve components changes as the fibers track from the elbow to the fingers. But until now, no one has pinpointed the degree of change precisely enough to improve surgical outcomes.

"Until now, fascicular repairs have had disappointing results, even with those who do the procedure routinely," says Greg Watchmaker, M.D., a resident in the department of surgery who developed the computer capability to study branching nerve patterns. "Incorrectly matched fascicles will grow improperly and impede restoration of function and sensory perception."

But researchers have discovered that the number of fascicles running through a nerve remains fairly constant over spans of one to two centimeters. They also found that fascicular branchings



The dissected nerve is suspended on a stainless steel frame and immersed in a cylinder full of formalin. Then it will be processed in alcohol and xylene.

While the gross anatomy of the median nerve was described at the turn of the century, recent attempts to define its internal structure have been few and limited, Watchmaker says. Sydney Sunderland's landmark article in 1945 provided the springboard for further studies, but "offered a hopeless proposition to successful realignment" in nerve repairs, especially over distances greater than three centimeters.

The median nerve has been the focal point of the Washington University investigation because one-third of all trauma involves the upper extremity and hand. The work has virtually limitless



The processed nerve is embedded in paraffin and sectioned in a microtome. Then the nerve sections are mounted on slides using a solution of water and white glue.

application in nerve reconstruction throughout the body, and investigators have recently begun to examine facial nerves.

In addition to the median nerve, the team has dissected one ulnar nerve and has started work on its first radial nerve. Investigators are continuing their study with examination of the facial nerve, which controls the muscles involved in facial expression. They hope to identify specific facial nerve components so that during surgical repairs or grafts, the correct nerve fibers return to the proper nerve muscle. Although work has just begun, researchers say the ability to map the facial nerve is expected to significantly improve surgical outcomes of facial repair due to injury or disease.

Defining the internal anatomy has been tedious, Washington University scientists say, but not without reward. They first created an extensive and precise database, studying 30 cadaver median nerves and sectioning them at

more frequent intervals than had been done previously.

"We wanted a database with a large number of nerves that would allow us to identify consistencies between individuals," Watchmaker says.

To preserve the internal makeup of the nerve during processing and sectioning, a silk strand was sewn into the delicate outer layer of the nerve to identify its top, bottom and sides. The position of the sutures helped in identifying slices when histologic sectioning was done to study structure and function. Investigators then painstakingly mapped the motor and sensory branches from their origin, recording whether they traveled above or below the level of the wrist, which was labeled point zero.

Equally time-consuming was the step-by-step processing of the nerves for histologic sectioning. A single nerve required several weeks of preparation, and even then there was no guarantee it would be suitable for study. One miscalculation in the lengthy dehydration process could destroy the nerve. To dehydrate the nerves, the spaghetti-like strands were tethered to a custom-designed long, stainless-steel carrier that was submerged in alcohol-based solutions.

The tissue was infiltrated with paraffin and cooled, and the processed nerve was cut into two-centimeter segments and embedded in paraffin blocks that could be sliced in segments thin enough to be examined through a microscope.



Slides are stained in a trichrome process requiring 20 separate baths.

Eleven nerves were sliced at one millimeter intervals and 16 specimens were sliced every 250 to 500 microns, or at one-half and one-quarter millimeter intervals. The ultra-thin sections were then affixed to slides and stained to provide definition of the fascicles.

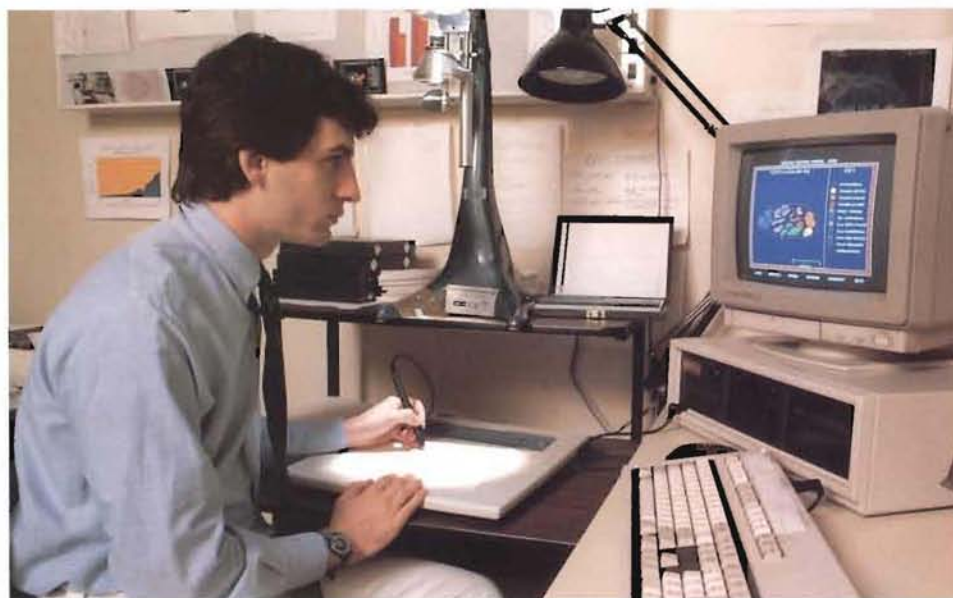
This approach enabled the team to identify the spatial relationships of fascicles and fascicular groups over the length of the entire nerve.

"It's a tedious project," Watchmaker comments. "It takes 10 days just to dissect and process specimens, and there's the chance they may not imbed in the paraffin. One mistake causes you to discard an entire limb."

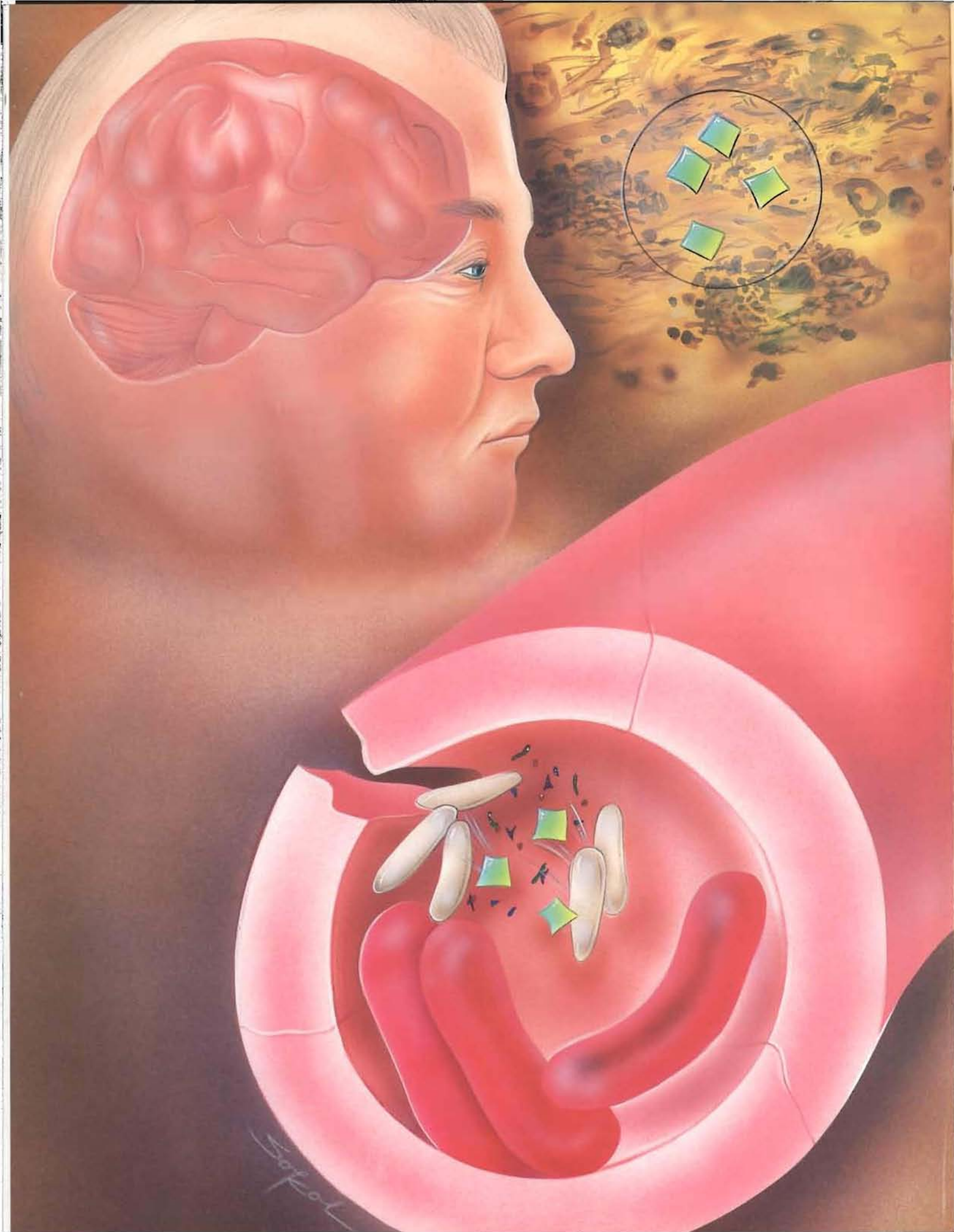
Because current biomedical software does not provide the capability to analyze the huge amount of data generated, investigators developed their own computer software. Watchmaker spent nine months designing a program to describe the fascicle outlines and coding their patterns (mixed or unmixed) for display. Refining the software has been an ongoing project that involves teaching the computer to accurately draw a smooth, digitized fascicle by picking the fewest number of points to describe the contour. Initially, the researchers and several medical students they recruited worked 15-hour days manually digitizing each fascicle bundle of each nerve section by applying pressure points with a pen. Using this method, they completed about 10 slides per hour. With the improvements, researchers have increased their output fivefold.

"Our ultimate goal is to create a computer database which can be accessed readily on a monitor during surgery," says Weeks. "When in the operating room working with two nerve ends that do not match exactly as determined by fascicular arrangement, both nerve ends will be digitized and the data base searched to identify matching fascicles. Then, the surgical repair can be performed."

Gumucio, one of the project collaborators, says the study could continue indefinitely. "If we are able to illustrate a much more detailed anatomy than before, there will be a major push to continue the research," Gumucio says. "Research up to this point has shown an anatomy that has gone from completely random to some form of organization to our rendition. With the success of our work, there is hope for more refined repair." ■



Finally, images of each nerve section are projected onto a digitizing tablet. Their outlines are traced with a digitizing pen and entered into a computer.



Sokol

Alzheimer's Research Gets A Boost

*Hematologists Elucidate
A Central Protein*

Activated platelets in the bloodstream are shown releasing a cascade of clotting agents, including one called factor XI_a-inhibitor. Investigations have shown factor XI_a-inhibitor to be a form of the precursor protein central to the formation of plaques common in the brains of Alzheimer's patients.

Hematologist George Broze, M.D., conducts research mindful of his mentor's philosophy that the subspecialty "concerns the blood and all of the organs through which it flows."

With that open-minded maxim as a guide, Broze pursues his investigations where they lead, coming into contact with research in many of medicine's various specialties. But always he has preserved his interest in blood and its fundamental nature. Quick on his scientific feet, he would be difficult to shock with an unexpected laboratory finding.

by Steve Kohler



George Broze, M.D.

DIFFICULT, BUT NOT IMPOSSIBLE. Shortly after Broze began advising post-doctoral fellow Raymond P. Smith, M.D., as the two were considering an appropriate project for Smith's attention, a serendipitous discovery surprised the lab. The finding marked what may turn out to be the biggest change in direction yet for Broze's research, and it catapulted the laboratory into the highly visible and competitive field of Alzheimer's disease research. Without anticipating it, the investigators identified both a source and a normal function for a protein that may be literally at the core of the disabling disease that impairs memory and progresses inexorably to severe dementia.

Working to classify the complicated interactions of proteins involved in blood clotting — a field in which Broze and his colleagues have become recognized experts — the researchers isolated a protein called "factor XIa-inhibitor." As a matter of course, the new protein was sent off to a medical school chemistry laboratory for a determination of the order of the amino acids along its molecular length and a search of computer databases to see if the protein had been identified previously in some other context. "We expected that we had a totally new protein, never isolated before," says Smith.

When the report came back, however, the lightbulb went on, illuminating a new direction for the lab. The protein Broze and his colleagues had purified — what

they called factor XIa inhibitor — was identified as a form of APP, for amyloid precursor protein. Present in many mammals and similar in a wide variety of species, APP is the source for the smaller amyloid protein central to the "plaques" found in the brains of Alzheimer's patients. Complex microscopic lesions, plaques are composed mostly of degenerated nerve cells often formed around a core of amyloid protein.

Precisely how the protein in the blood relates to Alzheimer's disease is not yet clear, but in exploring that question Smith has found a project worthy of his attention. If the link turns out to be fundamental, it suggests the possibility for a simple blood test to diagnose the disorder. Previously, no point of origin and no normal role were known for the protein. "This single observation has exploded into a new thrust for the lab," Smith says.

"Unexpectedly, this discovery brings together two disparate fields: the neurosciences, especially Alzheimer's research, and hematology, especially the study of coagulation," says Broze, an associate professor of medicine.

As they reported in a recent issue of the respected journal *Science*, the researchers found that platelets — disk-shaped elements in the blood that play a central role in clotting — contain a form of APP. In fact, Broze says, they now know that platelets are the main source of APP in the blood.

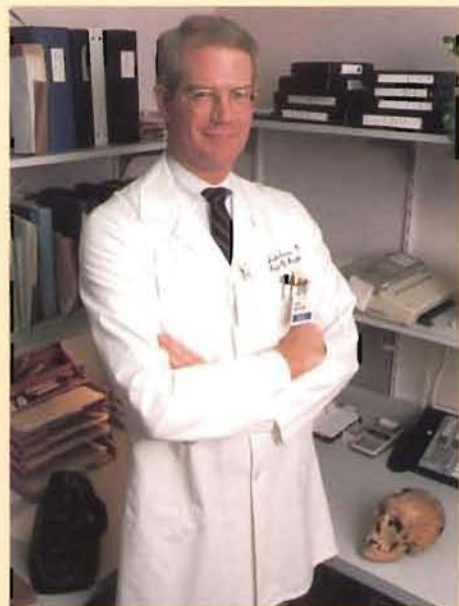
The findings also reveal for the first

time a physiological role for APP: As released by platelets, it functions to inhibit the action of factor XIa, one of many clotting agents. Broze thinks that APP may serve as a sort of balancing element, setting limits on the clotting work of the platelets. However, why platelets designed to stop bleeding also contain a coagulation inhibitor won't be finally determined until further research can be conducted.

To determine APP's role as a coagulation inhibitor, Broze, Smith and colleague, Darryl A. Higuchi, isolated the protein as one of the elements released by stimulated platelets. The investigators also purified a supply of the protein from liver cells. They then sent for the sequence of its amino acids and learned that it matched the sequence of APP, the precursor protein that is of such interest to Alzheimer's investigators.

Developing an antibody that reacted to the amyloid peptide, they confirmed its presence at one end of the protein released by the platelets. Broze says the functional clotting inhibitor (a region of 56 amino acids) and the amyloid protein found in Alzheimer's plaques (a peptide of 42 amino acids) are two distinct parts of the same big precursor protein.

Previous Alzheimer's research has shown that APP comes in three slightly different forms, depending on the number of amino acids that get spliced together. The shortest form — a total of 695 amino acids — is the most common in the brain. But sometimes, two longer forms get spliced, one of 751 and a second of 770



John Morris, M.D.

amino acids. These two contain the 56-amino acid domain that inhibits coagulation, Broze explains.

One faction of Alzheimer's researchers believes APP circulating in the blood is the source of the amyloid protein that becomes the core for the plaques in the brains of Alzheimer's patients. Broze thinks it is this group of scientists who will be most interested in his lab's work showing blood platelets as a source for APP.

If an overabundance of longer chain APP in the blood can someday be shown as a cause for Alzheimer's disease, a relatively simple blood assay could be devised to identify people at risk and provide a diagnostic test for the disorder, says John Morris, M.D., assistant professor of neurology and associate director of the Memory and Aging Project. Alzheimer's disease is difficult to diagnose, especially in its earliest stages when it most closely resembles age-associated memory impairment. Unfortunately, it is also in the early, mild stages that any treatment is likely to have its best effect. Estimates suggest that perhaps 10 percent of all people age 65 and older suffer from Alzheimer's.

Another group of Alzheimer's researchers theorizes that APP is the product not of the blood, but of brain cells themselves. Having shown that APP crosses cell membranes, these investigators propose that when the process goes awry the terminal peptide of 42 amino acids lodges at the edge of the membrane to form the core of a plaque.

Morris believes that Broze and Smith's work may have relevance for this camp too. Because the long form of APP works to inhibit clotting of the blood, he suggests, it is not hard to imagine that the protein also may have inhibitory function elsewhere, including the brain. He suggests that this function may prove important in modeling and refining synapses, connections where nerve cells communicate with each other. Disruption of the process could "disconnect" communications and potentially result in the dementia typical of Alzheimer's disease.

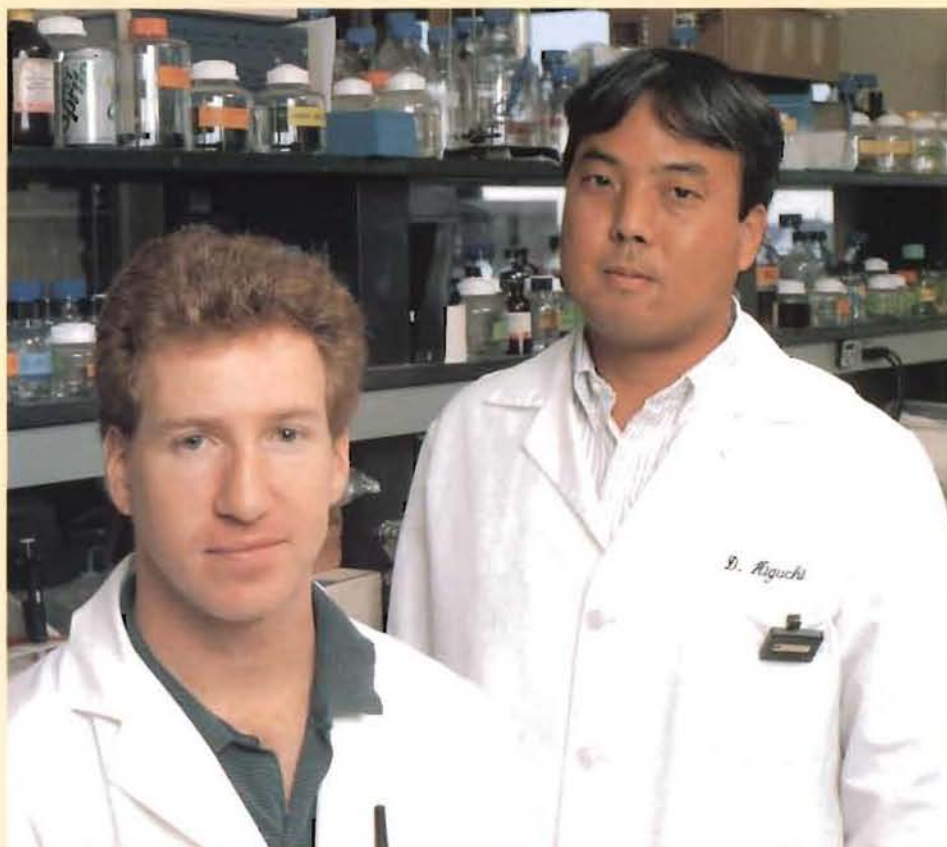
Before either possibility can be established, however, plaques will first have to be demonstrated to be a cause of Alzheimer's, a relationship not yet clear. Morris says plaques might just as easily be an effect of the disease, "but certainly one of the major lines of research into Alzheimer's disease investigates plaques and their constituents as central to its cau-

sation." Amyloid plaques in the brain, he says, are virtually universal in Alzheimer's disease but uncommon in normal aged brain.

One piece of evidence suggesting amyloid plaques as a cause for Alzheimer's can be found among Down syndrome patients, who develop both plaques and Alzheimer's disease at a much earlier age than others, Morris says. Down syndrome is attributable to an individual's inheritance of three (rather than the normal two) copies of chromosome 21, a condition called trisomy 21. The gene for APP

has begun into factor XIa's role in the brain and its effects on nerve cell growth.

Peter Walsh, M.D., Ph.D., professor of medicine and biochemistry and co-director of the Thrombosis Research Center at Temple University School of Medicine in Philadelphia, agrees that the link between a coagulation inhibitor and Alzheimer's is not clear. "But the magic of this situation is that George Broze realized what he had, recognizing its significance to another field," he says. "Here, in one step, he has identified the source for a central element. There may be no clear theories yet, but they will come."



Raymond P. Smith, M.D., left, and Darryl A. Higuchi

resides on chromosome 21, and the initial speculation was that trisomy 21 results in an overexpression of APP which then leads to the creation of plaques. This possibility seems unlikely for Alzheimer's disease not related to Down syndrome, Morris says.

The work by Broze, Smith and Higuchi represents the first step along what is becoming a broad avenue of Alzheimer's research. As a new direction, it provides more questions than answers. For the moment, Broze says, it is difficult to speculate accurately on just how the inhibition of a clotting agent relates to the pathogenesis of Alzheimer's disease. But research

Smith, too, expects "significant results from work that should now move quickly. Two independent camps, neurologists and hematologists, are working on it. That means lots of competition, but also lots of progress," he says. With APP's source in the blood identified and several projects underway to examine its physiological role in the brains of Alzheimer's patients, Broze believes, "We may be involved in this research for a long time," even if it is not what traditionally has been called hematology. ■

Carla E. Samson, M.D.



William G. Powderly, M.D.

UNCOMMON Responsibilities:

Training Physicians to Treat AIDS in the Community

by Steve Kohler

When she accepted her first critically ill AIDS patient in the fall of 1988, southern Illinois physician Carla Samson, M.D., worried about providing proper care. She never doubted her obligation to that patient, but she knew that

rare, medically challenging infections or malignancies might occur at any time. The medical possibilities went well beyond anything she had encountered previously in her family practice.

Support groups, hotlines and one-on-one counseling were available for AIDS patients, but what of their care givers? Where could a doctor go for reliable professional guidance and relief from the stress of treating a young patient dying of the era's most complicated medical problem?

Samson found the help she needed at the Washington University School of Medicine's AIDS Clinical Trials Unit (ACTU) in St. Louis. Of the 36 ACTUs in the U.S. — established and funded by the National Institutes of Health to be the front line in the nation's battle against AIDS — the Washington University

unit was the first to include an educational component that serves the needs of physicians.

"When we set up the unit, we took the perspective that the university has unusual resources and therefore uncommon responsibilities," says Barry A. Hong, Ph.D., director of the ACTU's Community Outreach and Consultation Program. That outreach program constitutes one part of the unit's activities, complementing scientific research and the clinical trials of promising treatments. "For the outreach component, we didn't want to duplicate the lay education that was already being done well," Hong says, "so we asked where our strengths could be built upon. What were the holes in the system?"

The answers to Hong's questions continue to evolve, but important among them is a system for assisting health care professionals in their confrontations with AIDS. To measure the need for such help, Hong, an assistant professor of medical psychology; Susan Wightman, R.N., the program coordinator; and their colleagues conducted a survey of physicians in Missouri.

The results, presented at the Fifth International Conference on AIDS in Montreal in June 1989, showed that

fully 46 percent of the doctors in Missouri had no firsthand experience with human immunodeficiency virus (HIV) infections. HIV is the microorganism that infects and defeats the human immune system, leaving the body open to the infections that characterize AIDS. Only one percent of the respondents had cared for more than 10 AIDS patients. The State of Missouri estimates that there are 12,000 to 15,000 residents infected with HIV, but only about 2,400 of those can be contacted.

The scientists concluded that medical education and consultation are vital in low-prevalence areas — those that are not on major illegal drug distribution routes or those with smaller, less visible gay populations. Intravenous drug users and homosexual men are most at risk for AIDS, though the problem honors no distinctions.

Education is crucial, Wightman says, because no place is likely to remain a low-prevalence area for long. Tracking figures from the Center for Disease Control (CDC), she reports that early estimates of the number of AIDS cases may have been low, with predictions erring by as much as 20 percent.

Nationally, the number of cases is now expected to rise by 10,000 per year,

"Some doctors refuse AIDS patients, saying they're not qualified to treat them. I say they'll just have to get qualified."

from 39,000 new cases in 1988 to 80,000 new diagnoses in 1992. About 146,000 AIDS cases have already been reported to the CDC, with an estimated 55,000 people currently under care. By 1992, the figures are expected to approach 365,000 diagnosed cases and 172,000 requiring care.

Washington University's program offers help in several forms to physicians confronting this epidemic. In Samson's case, her specific question about the protocol for respiration therapy for a patient with pneumocystis carinii pneumonia (a common infection in AIDS patients) was answered over the consultation phone line that provides access to specialists — hematologists, infectious disease experts, virologists, psychiatrists, and many others — at the School of Medicine. Samson says of the telephone service, "It's been a godsend. I used it as recently as last month when I treated an HIV-positive patient allergic to sulfa drugs."

Additionally, William G. Powderly, M.D., clinical director of the ACTU, and several staff members travel to downstate Illinois and outstate Missouri to present grand rounds for physicians of those areas. At those sessions, specific questions are answered by the experts, and "we get a good general understanding, too," Samson says.

As a result of her interaction with the outreach program, Samson's practice has developed a flow chart to manage the progress of HIV-positive patients. Procedures in the office have also been examined, and changes have been made. "We take universal precautions, now," Samson says.

All members of the ACTU team, from bench scientists to clinicians, take part in such visits and speaking engagements, interpreting research and its goals and answering questions. "It's not the usual sort of thing a school of medicine does," says Hong, "but it

raises good questions about what our role should be and what our obligations are. It has thrown us into the community and made us highly visible. It has certainly eliminated any concept of the university as an ivory tower on the issue of AIDS."

Scientist-physicians from the ACTU are regularly called upon to serve as medical advisors for organizations dedicated to the fight against AIDS. Hong currently serves as chairman of the St. Louis AIDS Network, an amalgamation of groups that work on joint projects and share information. "The university is being used as a bridge, as a buffer between people who would otherwise never get together," says Hong.

To further spread accurate information to health care workers, the outreach program publishes a newsletter three times each year, and Wightman organizes educational events that attract primary care physicians, nurses, and social workers. Full-day symposia, like the one held October 26, 1990, in St. Louis, are also conducted in rural parts of Missouri and Illinois. A care manual is being prepared as a resource for doctors, and 55 speaking engagements were fulfilled last year.

But beyond the obvious need for all care givers to be familiar with the intricacies of the complicated syndrome that is one of the nation's foremost health concerns, such education is important for other reasons, too. Jake, an AIDS patient in his 30s who has just had to resign from his job because of increasingly difficult bouts with dementia, says "It's important to me that I don't have to go far to get my treatment. Soon, I may not be able to travel. And this is my home." Hong comments that a patient's care is delivered most effectively in a familiar environment, with the support of family and friends whenever possible.

At Bethany Place, a resource center for AIDS patients in Belleville, Illinois, the business card of the outreach program is pinned to the bulletin board along with those of perhaps 50 other resources. Sister Mary Ellen Rombach and Sister Carol Baltosiewicz, two Franciscan nuns who experienced separate callings to help AIDS patients and subsequently founded Bethany Place, use the phone number on the card whenever a doctor calls to say he needs help treating an AIDS patient. It is a common occurrence, they say.

Sister Baltosiewicz also thinks the

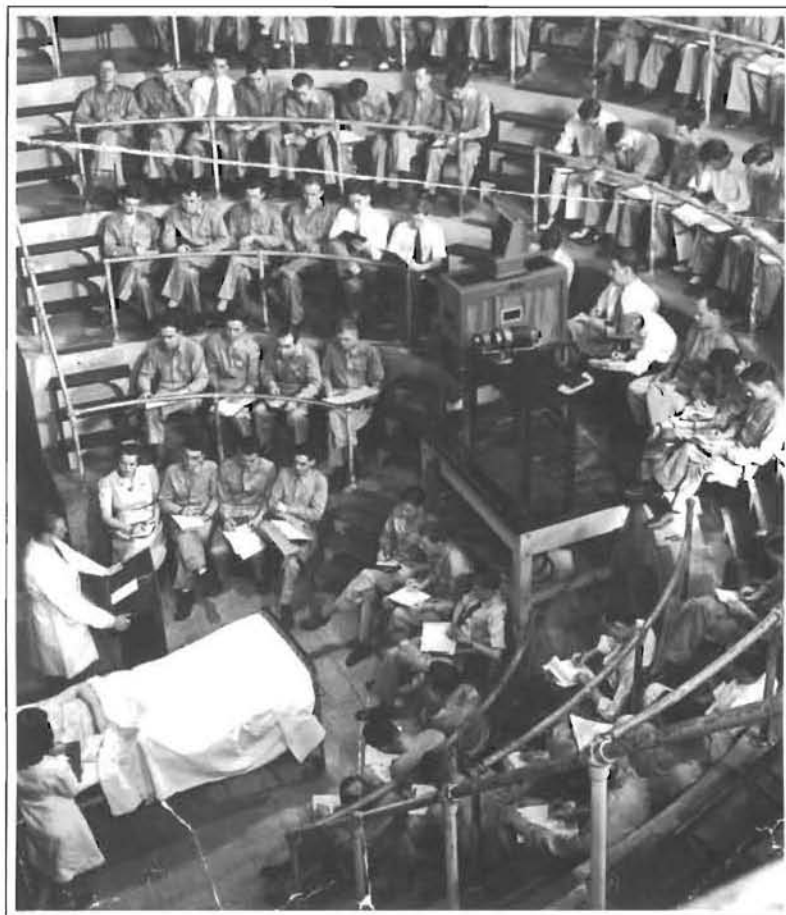
information provided by the outreach program is her best weapon in the fight to defuse the fear expressed by some physicians working in what she calls a "conservative, reserved region." She says, "Some of our doctors just won't treat AIDS patients. They refuse out of fear of infection, homophobia, and probably some concern that as patients get sicker, they won't be able to pay all their bills." Appropriate education will help the Sisters overcome such refusals, they hope.

Sister Rombach and Sister Baltosiewicz believe that the numbers of cases looming ahead mean that soon, doctors won't be able to refuse to accept AIDS patients. They say that many of their clients are returning to their homes in the Midwest's smaller cities from Chicago and the coasts as their conditions worsen. "They're literally coming home to die," says Sister Rombach. Major treatment centers in metropolitan areas would soon be overwhelmed if communities did not care for their own: "AIDS is a community disease. The community will have to learn to treat it like other chronic diseases," Sister Baltosiewicz says.

In San Francisco, where a large proportion of the population is infected with HIV, the care of patients is already pressing the limits of the health care system, according to Paul A. Volberding, M.D., who heads the AIDS clinic at San Francisco General Hospital. There will be an even heavier burden as the care of early HIV disease increases, and Volberding says testing in larger numbers will bring powerful impacts to cities like St. Louis. "The epidemic will continue to expand. What we must establish is a system prepared to treat thousands," Volberding says. "That system will have to use the resources available in the patients' communities." Volberding, an associate professor of medicine at the University of California at San Francisco, oversees the treatment center that has provided care to at least one-third of the city's 8,500-plus cases of AIDS.

And Carla Samson, whose group practice now treats eight AIDS patients but may soon treat many more, says she strives to maintain their health "and a place of comfort." She would not be able to send those patients away for the help they need: "To turn my back would be unethical." She adds, "Some doctors refuse AIDS patients, saying they're not qualified to treat them. I say they'll just have to get qualified." ■

"Medical School Militarized" read the headline over this Post-Dispatch photo; it showed Dr. Carl Moore lecturing to a group of medical students in army uniforms, on August 22, 1943 — the only year the School of Medicine graduated two classes with an accelerated program to meet World War II medical needs.



Washington University School of Medicine has one of the richest traditions of any medical school in the country. The School was formed in 1891 when the St. Louis Medical College, which had been founded in 1842, became the Medical Department of Washington University. The last 100 years have been rich in important events and the following pages contain some of the highlights. Future issues of Outlook will feature more memorable moments in the life of this great institution.

by Marion Hunt



The young Dr.
Joseph Erlanger,
first Professor of
Physiology, seated
at his desk in 1910.

In April 1915,
Robert Brookings
sat in full academic
regalia, listening to
a dedication speech
for the new medical
school buildings —
as yet unfinished.
To his left are Dr.
William Welch
and Mr. Edward
Mallinckrodt.



April 14, 1891

Under an ordinance enacted this day, the Medical Department of Washington University was established to be known as St. Louis Medical College and staffed by its faculty.

March 1892

At the 50th commencement of the St. Louis Medical College, Chancellor W.S. Chaplin conferred the first medical diplomas from Washington University on 19 graduates.

September 1892

A new four-story building for the Medical Department was opened at 1806-14 Locust Street.

November 9, 1895

Robert S. Brookings was elected President of the Corporation of Washington University, a post he was to hold for the next 33 years.

Summer 1897

The faculty ruled that henceforth four years of study would be required to obtain an M.D.

April 27, 1899

At commencement, the announcement was made of the union between the Missouri Medical College and the St. Louis Medical College under the auspices of Washington University.

May 1, 1899

The faculty members of the St. Louis Medical College held their last meeting as a separate institution, disbanding with this resolution: "May the hope that animates ... this action find its fruition in the building up of a Medical Department of Washing-



In 1917, a group of young surgeons in Army uniforms prepared to leave the School of Medicine for the battlefields of France.

ton University that shall prove worthy of the heritage they bequeath it."

May 22, 1899

The University's Board of Directors approved the union between the two oldest medical schools west of the Mississippi to be known as the Medical Department of Washington University.

April 27, 1903

An ordinance was approved by the Corporation establishing a Washington University Lying-in Hospital of 20 beds for the exclusive use of the Medical Department. Located in the old Missouri Medical College building,

it was a first step toward assuring clinical instruction for the medical students.

March 5, 1906

Robert Brookings announced that he and Adolphus Busch had given the necessary funds to pay the Medical Department's accumulated debt of \$51,000. The Board of Directors approved a new ordinance extending university control to include the Medical Department's finances and providing that the Department should be "in every respect under the general supervision and control of Washington University."

April 1909

Abraham Flexner made his first trip to St. Louis to gather information for his Report on Medical Education. He found the Medical Department at Washington University "a little better than the worst I had seen elsewhere, but absolutely inadequate in every essential respect ... there is no 'team work', no training in method, no governing purpose." Robert Brookings' reaction to this evaluation was indignation; he took the first train to New York for a meeting with Flexner who agreed to return to St. Louis.



The front of the new St. Louis Maternity Hospital as it looked on May 13, 1926.



Dr. Barry Wood,
Head of Medicine,
discussing a case
during staff rounds
in 1943.

May 1909

Brookings toured the Medical Department with Flexner and agreed with his findings; he arranged for Flexner to meet with the Board of Directors. Flexner advised them to form a new faculty, raise an endowment, and reorganize the clinical facilities.

May 31, 1909

The Medical Department's faculty considered reorganization at its annual meeting. Dr. Robert Terry made a motion that it "is the wish of the Medical Department that there be a reorganization of the teaching corps and curriculum of the Medical School and that this reorganization be placed in the hands of the Chancellor and Board of Directors." The motion was unanimously carried.

July 30, 1909

Nineteen members of the medical school faculty resigned to make room for a new group of professors, then being recruited by Robert Brookings from across the country. Only Dr. Robert Terry was retained as head of Anatomy.

September 1909

The new Executive Faculty of the reorganized

Washington University School of Medicine met as a body for the first time with Dr. George Dock, head of Medicine, as its Dean. His colleagues were Dr. Robert Terry (Anatomy), Dr. Philip Shaffer (Biochemistry), Dr. Joseph Erlanger (Physiology), and Dr. Eugene Opie (Pathology). Committees were appointed to supervise admissions, curriculum, the library, buildings, and the catalogue.

October 14, 1909

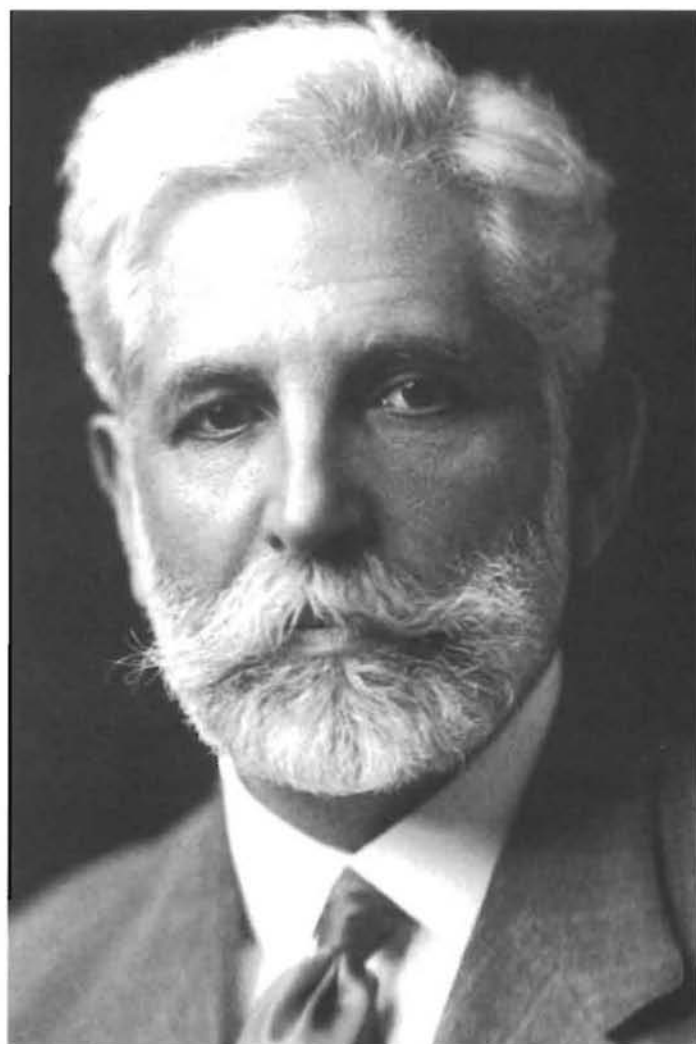
Chancellor David Houston appointed a Reorganization Committee from the Board of Directors composed of Brookings' closest friends: Edward Mallinckrodt, W.K. Bixby, and Robert McKittrick Jones.

November 1909

Flexner paid another visit to St. Louis to make more criticisms and suggestions about how best to achieve an effective reorganization.

December 29, 1909

Robert Brookings wrote to Henry Pritchett, head of the Carnegie Foundation, saying that his own personal fortune would not be sufficient to accomplish the necessary reorganization: "I am in despair of accomplishing anything unless some man



Robert S. Brookings

like Mr. Carnegie or Mr. Rockefeller, who could do a thing of this kind without feeling it, would be interested ... If I had the money, I would not permit any other man in the country to have a hand in it."

January 20, 1910

Robert Brookings pledged a large part of his personal fortune "to gather together a group of scientific men of such acknowledged ability as to ensure to the West and Southwest, and more especially to St. Louis and the State of Missouri, a medical school and hospitals of the first rank..."

April 28, 1910

Mr. Brookings announced that subscriptions of \$40,000 had been pledged toward the annual fund by himself and William Bixby, Edward Mallinckrodt, and Adolphus Busch. The new medical school faculty was taking shape: Dr. Joseph Erlanger, Dr. Eugene Opie, Dr. George Dock, and Dr. Robert Terry had agreed to take positions.

June 7, 1910

The Corporation of Washington University passed an ordinance formally changing the name of the Medical Department to the Washington University School of Medicine. This coincided with the Flexner Report's publication; the statement about Washington University had been revised to read: "Washington University is...marked out as the natural patron of medical education in Missouri. Its importance is bound to be more than local...There is abundant evidence to indicate that those interested in



Dr. Carl Cori and Dr. Gerty Cori in their laboratory at the time their Nobel prize was announced in 1947.

Washington University appreciate its 'manifest destiny'; it bids fair shortly to possess faculty, laboratories, and hospital conforming in every respect to ideal standards."

October 28, 1911

The Trustees of the Robert Barnes estate entered into an affiliation agreement with the School of Medicine to construct a hospital that would become a teaching institution on a site near the new medical school buildings.

July 3, 1912

Robert Brookings pledged an additional \$1,000,000 toward the new medical school buildings.

July 8, 1912

The women managers of St. Louis Children's Hospital signed an affiliation contract with the medical school, agreeing to become a teaching hospital relocated on a site adjacent to Barnes Hospital and the School of Medicine.

May 17, 1913

The cornerstone was laid for the North Laboratory Building, the first element in the new medical complex.

November 19, 1913

Robert Brookings called a special meeting of the Executive Faculty to announce that he was applying to the General Education Board for grants to place three clinical departments (Medical, Surgery, and Pediatrics) on a full-time academic basis.

January 12, 1914

Robert Brookings submitted an application to the General Education Board.

February 10, 1914

The School of Medicine received a \$750,000 grant from the General Education to establish the full-time system in the first three clinical departments.

October 27, 1914

The dedication of the new Barnes Hospital marked the opening of the medical school's first affiliated teaching institution.

January 9, 1915

The relocated St. Louis Children's Hospital was dedicated.

April 28, 1915

A three day celebration and dedication of the medical school's new North and South Buildings was held, along with special ceremonies honoring the two affiliated hospitals. Robert Brookings spoke: "We hope that our efforts will contribute, in some measure, to raising the standard of medical education...and that we will add, through research activities, our fair quota to the sum of the world's knowledge of medicine."

July 1, 1916

The full-time plan became effective for the Department of Medicine. The Department of Surgery followed on January 1, 1917, and Pediatrics on July 1, 1917. Robert Brookings explained his commitment to this plan for the medical school, noting: "The best service rendered the world

Dr. Lauren Ackerman, Head of Surgical Pathology, examining specimens with members of his staff in 1955.



has, by necessity, led men to give themselves without reserve, and has more often been accomplished by financial sacrifice than by gain."

April 27, 1917

Base Hospital 21, organized from the staff of the Washington University School of Medicine and accompanied by nurses from Barnes and Children's, was mobilized and sent to France. The staff served 65,563 patients in 18 months of work.

April 3, 1918

The Executive Faculty voted to admit women to the School of Medicine; women house officers were accepted for the first time in the Department of Pediatrics. That fall, Carol Skinner Cole was the first woman admitted as a regular student.

June 4, 1921

Faye Cashatt Lewis, a transfer student, became the first woman to receive the M.D. from Washington University.

April 26, 1923

An affiliation contract was signed between Washington University and the St. Louis Maternity Hospital — the first step in establishing adequate teaching facilities for a full-time Department of Obstetrics and Gynecology.

November 22, 1923

The General Education Board authorized payment of \$650,000 to the Washington University Medical School endowment to put the Department of Obstetrics on a full-time basis.

February 1, 1924

Dr. Evarts Graham, Bixby Professor of Surgery, in collaboration with Dr. Sherwood Moore, Dr. Glover Copher, and Dr. Warren Cole, achieved the first visualization of the gall-bladder.

March 19, 1927

The General Education Board agreed to give \$750,000 to help establish a full-time Department of Radiology. Mr. Edward Mallinckrodt donated \$250,000 for a new building to house the Department.

August 1, 1927

The new St. Louis Maternity Hospital, relocated near Barnes Hospital, opened its doors to patients.

May 24, 1928

The General Education Board gave \$400,000 to establish a full-time Department of Ophthalmology.

January 1929

Mrs. Oscar Johnson and her sons gave \$500,000 to construct "a coordinated building consisting of an institute of eye research and teaching in ophthalmology and otolaryngology and of the McMillan Eye, Ear, Nose and Throat Hospital." The Rand Johnson Building would be opened in stages from 1931 to 1943.

June 11, 1929

Robert Brookings was awarded an honorary M.D. as well as an L.L.D. from Washington University, the first to be so honored.

October 2, 1930

The cornerstone for the Mallinckrodt Institute was laid.

July 15, 1931

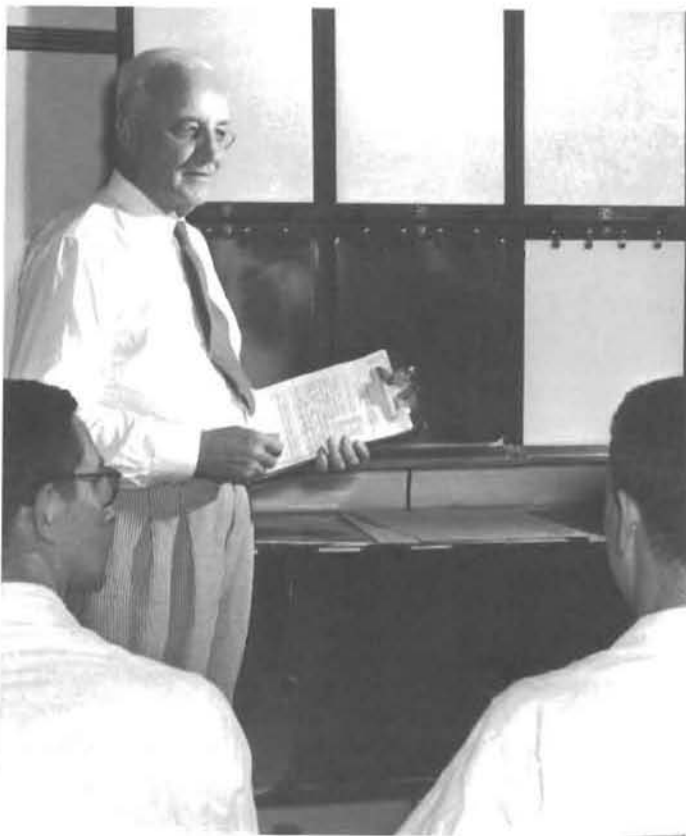
The McMillan Hospital clinics for eye, ear, nose and throat patients were opened. Due to the depression, the building itself would not be completed until 1943.

April 5, 1933

Dr. Evarts Graham performed the first successful pneumonectomy, thereby opening a new era in thoracic surgery.

May 20, 1938

The Rockefeller Foundation made a three-year grant to help support a full-time Department of Psychiatry.



Dr. Evarts Graham reviewing cases with younger members of the medical staff in 1950.

December 11, 1941

The Executive Faculty recommended adoption of an 11-month class schedule to graduate doctors in three years for the duration of the war.

January 10, 1942

The 21st General Hospital, successor to Base Hospital 21, was activated for service in France with doctors and nurses drawn from the medical school and hospital staffs.

October 15, 1943

The McMillan Hospital was opened.

October 26, 1944

Professor Joseph Erlanger received notice that he would share the Nobel Prize in Physiology and Medicine

with Dr. Herbert Gasser for their work on the highly differentiated functions of nerve fibres.

October 23, 1947

Dr. Carl Cori and Dr. Gerty Cori were awarded the Nobel Prize in Physiology and Medicine for their collaborative work elucidating "the source of the catalytic conversion of glycogen." Dr. Gerty Cori thus became the first American woman ever to receive the Nobel prize.

March 11, 1948

Trustees of the Barnard Free Skin and Cancer Hospital signed articles of affiliation with Washington University, agreeing to relocate within the medical center.

February 21, 1950

The centennial of Robert Brookings' birth was celebrated with a convocation in Graham Chapel where Abraham Flexner, Ernest Goodpasture, Edwards Park, and Charles Huggins were awarded honorary degrees. That same day, the cornerstone was laid for the new Cancer Research Building with the Surgeon General of the United States presiding.

March 9, 1950

The contract for the new Wohl Hospital, given by Mr. and Mrs. David P. Wohl in memory of their son, was let; the new building would house the Departments of Medicine and Surgery.

July 1950

Wallace Renard pledged \$350,000 to assist in the construction of a 100-bed psychiatric hospital.

June 24, 1954

Daniel Nathans became the first graduate of the

Washington University Medical School to be awarded his medical degree *magna cum laude*.

October 10, 1954

The new Barnard Free Skin and Cancer Hospital was dedicated.

June 4, 1962

James L. Sweatt III became the first Afro-American graduate of the Washington University School of Medicine.

February 10, 1966

James S. McDonnell announced the gift of \$4,000,000 to construct a new Medical Sciences Building.

September 10, 1967

A formal "launching" was held for the McDonnell Medical Sciences Building.

April 2, 1969

The Washington University School of Medicine announced that it would award an honorary M.D. to James S. McDonnell, the second person to be so honored (the first was his distinguished predecessor in philanthropy, Robert Brookings forty years earlier.)

October 17, 1970

The McDonnell Medical Sciences Building was dedicated.

December 1971

Dr. Earl Sutherland, M.D. Class of 1942, whose research began in Dr. Carl Cori's laboratory, became the 40th American to win the Nobel prize in Physiology and Medicine.

December 13, 1975

James S. McDonnell announced the gift of funds

sufficient to endow a new Department of Genetics.

December 1978

Dr. Daniel Nathans, M.D. Class of 1954, shared the Nobel Prize in Physiology and Medicine; his research interests began in the laboratory of Dr. Oliver Lowry, Department of Pharmacology.

July 13, 1979

James S. McDonnell endowed a Laboratory of Biochemical Genetics.

May 1980

Shortly before his death, Mr. McDonnell endowed the McDonnell Center for Higher Brain Function.

September 8, 1983

The McDonnell Foundation endowed a new Center for Cellular and Molecular Neurobiology.

September 14, 1983

A Centennial Symposium in honor of Dr. Evarts Graham was held, attended by many former students and colleagues.

April 1984

A new building for St. Louis Children's Hospital opened.

October 15, 1984

The Clinical Sciences Research Building, with 382,000 square feet of space for laboratories, was dedicated.

Summer 1989

The new Biomedical Communications Center and Library was opened.

October 3, 1990

The Washington University School of Medicine was designated one of four national centers of investigation for the Human Genome Project.



Dr. William H. Danforth, then Vice Chancellor of Medical Affairs, speaking at the "launching" of the McDonnell Medical Sciences Building in 1967.

A Pediatrician At Heart

Associate Dean John C. Herweg Retires After 25 Years of Serving Students

by Robert Lowes

Student class shows will never be the same now that John C. Herweg, M.D., '45, retired after 25 years in the post of associate dean of the School of Medicine.

Herweg was a fixture in the annual productions, either as a cameo performer — a Boy Scout leader playing reveille on a trumpet, for example — or as someone whom students impersonated. Perhaps they found the nattily-dressed, courtly and ever cheerful collector of turtle replicas a ripe target for good-natured satire. At the same time, they were paying tribute to an educator turned friend and father-figure.

As associate dean, Herweg was deeply involved in the lives of medical students — selecting them, finding financial aid for their educations and holding their hands during the ups and downs of four challenging years. The fact that Herweg is a pediatrician helps explain his relish for the job.

"I've always thought that I was practicing pediatrics with an older age group," says Herweg. "I've dealt with such bright young people. That's been the joy of it."

Herweg officially retired at the end of June, but in one sense, he will continue to cultivate medical careers. A four-year, full-tuition scholarship has been created in Herweg's honor as part

of the new Distinguished Alumni Scholarship Program. Unrestricted alumni contributions will fund approximately 70 percent of the scholarship, with the School of Medicine supplying the rest.

Over the last 25 years, Herweg's "pediatric" caseload has numbered approximately 2,500 students, and their presence at the School of Medicine was due in large part to Herweg's role as chairman of the admissions committee. Its responsibility is immense, as evidenced in the 1990 selection process.

Some 3,550 inquiries were received for 120 spots in this fall's first-year class, with 2,700 students actually completing applications. The 22-person committee interviewed just under one-third of the applicants. As always, Herweg interviewed more students than anyone else. Approximately 350 students were accepted; roughly two-thirds chose other medical schools, frequently for geographical reasons, says Herweg.

"If you grew up next to an ocean, you'll find there's no place to surf here," says Herweg. "If you grew up with mountains 30 minutes from home, well, we don't have them."

M. Kenton King, M.D., dean of the School of Medicine from 1965 to 1989, calls Herweg "the most knowledgeable person in the coun-

try about medical-school admissions."

"He has maintained a very high standard for admissions to this school," says King, adding that Herweg led the way in admitting more women and minority students.

Herweg also took on the sometimes delicate task of interviewing applicants who are sons and daughters of alumni. They are the only applicants the committee interviews twice. If the admissions committee turns them down, "I share the onus of the decision," says Herweg.

It takes more than reviewing a college transcript to size up a medical-school applicant, according to Herweg.

"We try to assess their maturity. Do they have the personal characteristics that will help them relate to a wide range of people in a short period of time? What are their conversational skills? Are they able to speak on a wide range of subjects?"

"Somewhere along the line we focus on motivation. The standard answer is, 'I like science and I want to work with people.'"

While they are generally a well-adjusted lot, medical students still need nurturing. During his tenure as associate dean, Herweg maintained an open-door policy — and a well-known routine.

"He always greets the students, shakes their hands, makes sure they're seated, and then pulls up his chair

next to them," says John F. Walters, assistant dean for student affairs.

John T. Oldham, M.D., '78, remembers Herweg from his few office visits as a "very pleasant, very consoling type person." Oldham, who is now an emergency room physician in St. Louis, says Herweg didn't always grant every wish, "but you felt good afterwards."

Some concerns that Herweg treated in his desk-side manner were as simple as juggling an academic schedule. Other times, the problems were more personal.

"Some students get down and they need to be encouraged," says Herweg. "With others, you have to apply some stimulus so they will get with it."

As a member of the Committee on Academic Review and Promotions, Herweg occasionally was the bearer of bad news to the struggling student who would be dropped from the program. "It is never pleasant to talk with students who are in academic difficulty," says Herweg, adding, "Somebody has to do it."

At the same time, Herweg signed hundreds of letters a year congratulating students who performed honors-level work. He also took the time to send handwritten notes of condolence to students when a parent or loved one died.

Herweg chaired the



John C. Herweg, M.D., and his wife, Dorothy, spend much of their newfound free time bird watching around the world.

school's financial-aid committee, but more often than not, he heard about students' monetary fixes firsthand as treasurer of the alumni association. Herweg issued loans of up to \$1,000 from the association's emergency fund to students who were strapped for cash. Sometimes a student needed air fare to attend a funeral. Or, as was the case with second-year student James J. Stevermer, a financial-aid check was late in the mail.

"He was very understanding and cooperative," says Stevermer, who hails from Easton, Minn. "In five minutes, he gave me the okay to get the loan."

Besides serving 25 years as associate dean, Herweg also was assistant dean, of postgraduate education from 1952 to 1960, helping physicians who served in World War II refurbish clinical skills. However, Herweg originally entered medicine not to train others for the

field, but to practice it. What was *his* motivation?

Herweg smiles, "That's what you discuss with every medical school applicant."

Born in Fort Dodge, Iowa, Herweg contracted measles at the age of 3, followed by pneumonia and empyema, an infection that killed multitudes during the influenza epidemic of World War I. "I suspect (the illnesses) had something to do with it," Herweg says about his desire to practice medicine. "I admired physicians and felt that I wanted to be one."

Pediatrics appealed to him because children represented "the future." When he walked into the wards of St. Louis Children's Hospital for the first time, "it seemed to have an attractive aura."

Herweg earned his M.D. at the School of Medicine in 1945 and completed his pediatrics residency at St. Louis Children's Hospital. For a short time, he and his first wife Janet, also a pediatri-

cian, practiced together in Monroe, Wis. Herweg came back to the School of Medicine in 1951 to teach, eventually becoming professor of pediatrics in 1972.

It was shortly after his return to St. Louis that the illnesses he battled in the hospital ravaged his own family. His daughter Judy, the first-born of his four children, died of leukemia in 1954. His father James died suddenly in 1956. And in 1958, his wife Janet died after a two-year struggle with cancer.

"Fortunately for me and the children, Janet and I knew my present wife, Dorothy, who was the head nurse in the infants ward at St. Louis Children's Hospital. I convinced her to trade the responsibility of 32 babies for three school-age children.

"She salvaged four lives."

Over the years, Herweg's practice of pediatrics was increasingly constrained by teaching and administrative

duties, but he nevertheless excelled in that specialty. "He was such an accomplished pediatrician, he took care of a significant number of children of faculty, says M. Kenton King. "That's always the best mark of a good doctor, if other doctors take their families to him."

The long-time associate dean lugged paperwork home with him, but he balanced his vocation with refreshing avocations. He and his wife Dorothy tend a 20-foot-by-30-foot garden of flowers and salad vegetables. They're also avid birdwatchers who scan the treetops for wing markings whether they're roaming Washington University's Tyson Research Center or a foreign country. In February, they visited the Galapagos islands of Charles Darwin fame and notched their binoculars with sightings of the blue-footed booby and Darwin finches.

Then there are those ceramic and stone turtles that sat on countertops and piles of paper in Herweg's old office.

"I like turtles," Herweg says, smiling, "They're slow and methodical, but they get there."

Now that he has retired, both he and wife Dorothy will continue to collect turtles and study birds in more far-flung travels. On the home front, Herweg says, he'll probably spend three years cleaning out his basement.

And maybe someone will invite him back to a student class show so he can accept an honorary award — not an Oscar, but a Turtle — for his lifetime achievement as a good sport. ■

The Alumni Report

Dr. William Dock Dies at 91

By Marion Hunt

When Dr. William Dock died at the age of 91 on October 17, 1990, The New York Times called him "an innovator who questioned medical beliefs." In the mid-1930s, he criticized the then common practice of prolonged bed rest, concluding that it "kills more patients than anesthesia and all other drugs." By the 1940s, he was warning of danger from high-fat diets. In 1979, at the

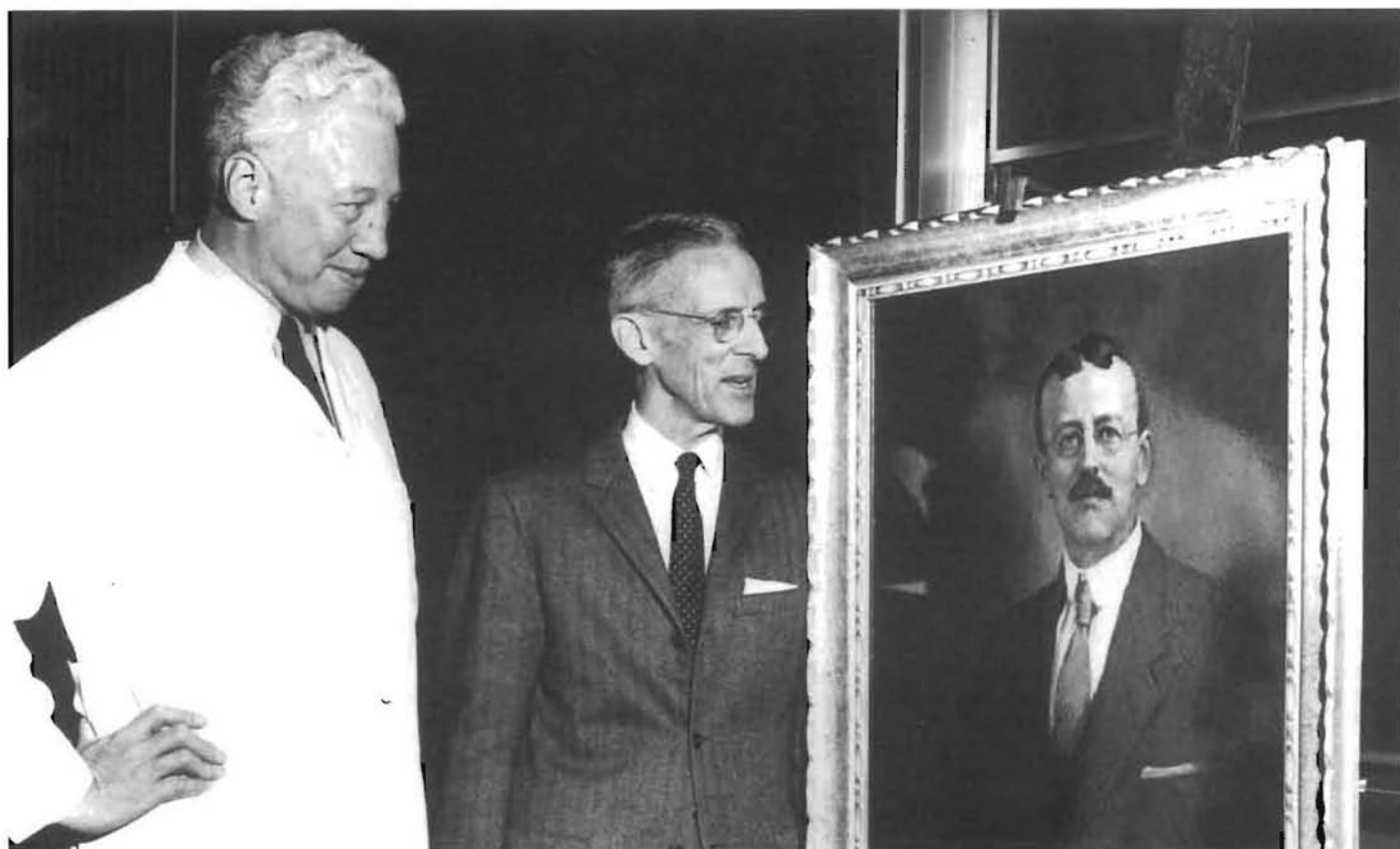
age of 81, he published original research on Korotkoff's sounds in The New England Journal of Medicine. Dock attended Washington University School of Medicine from 1919-1921 and received his medical degree from Rush Medical College in 1923.

Dock's lifelong attitude of inquiry would have pleased his father, Dr. George Dock, the first full-time head of Medicine at Washington University from 1910 to

1922. When William Dock was a boy, Robert Brookings often came to dinner to discuss plans for the new medical school buildings. The younger Dock graduated from Washington University in 1920, with time out to drive a French army ambulance – for which he received the Croix de Guerre, a military decoration awarded for gallant action in war.

After two years at the Washington University

School of Medicine, he transferred to Rush Medical College for clinical training. The reason was simple: he wanted to avoid any chance of being treated as the Professor of Medicine's son. George Dock encouraged such healthy independence and never interfered with his son's medical career. Indeed, when asked by a fellow physician how to make his son into a doctor, the senior Dock replied: "We're only the envelopes in



William Dock, M.D., presenting a portrait of his father, George Dock, M.D., to Carl V. Moore, M.D., head of the Department of Medicine in 1963.

which the information is delivered"

— an answer his own doctor son quoted with delight.

William Dock received his M.D. in 1923 and was a house officer at Peter Bent Brigham with Dr. Samuel B. Grant, WUMS Class of 1920, a lifelong friend. In 1926, he joined Stanford's Department of Medicine and was made head of Pathology in 1936, resigning in 1941 to take a similar position at Cornell. In 1944, he was appointed head of Medicine at the Long Island College of Medicine (now SUNY Downstate Medical Center). Dr. Dock retired from his academic position in 1963, but continued working until 1979 when he settled in Paris, France. A former president of the American Society of Clinical Investigation, and a Master of the American College of Physicians, he said simply: "My greatest pride is in having helped to bring better medical care to the community."

Though he did not stay for his M.D., Dr. Dock always enjoyed returning to the Washington University School of Medicine; his loyalty ran deep. He remembered his preclinical teachers as outstanding: Drs. Shaffer, Gasser, Erlanger, and Terry. In 1954 he was graduation speaker; in 1963, Dr. Carl Moore invited him to serve as a visiting professor of medicine. On this occasion, he presented a portrait of his father to the School. Dr. Dock returned for the last time in 1984, bringing a rare book for the library's collection.

Two generations of medical students remember him

as an inspired and inspiring teacher. His ward rounds were described as "Halley's comet sweeping along with a train of earnest young doctors eager to assimilate his very lucid and dramatic case presentations." For him, teaching was an essential part of medicine. "We have to teach patients to live with their diseases, and all physicians, if they are any good, are teachers." In 1944, Dr. George Dock assessed his son with characteristic clinical acumen: "Bill has always been serious about patients and students, but he is casual

about administrative chores and downright flippant about research." Despite this irreverent attitude, Dr. Dock authored 196 articles and 2 books — the second, published when he was 85, concerned preventing arterial obstruction.

At Downstate, he is remembered with the annual William Dock Master Teaching Award. Last year's winner was Dr. Stephen LeFrak, Professor of Medicine at the Washington University School of Medicine and a Downstate alumnus. He recalls Dr. Dock's patience

with students and the dramatic finale of his last lecture when he tossed his stethoscope into the audience. Students competed to catch it like a World Series baseball. It was certainly the medical equivalent.

Dr. Dock is survived by two sons, George of Portland, Oregon, and Christopher of Guadeloupe, and a nephew, Dr. Donald Dock of Branford, Connecticut. ■

CLASS NOTES

'40s

An endowment has been established in honor of **Ewald W. Busse, M.D. '42**, for his three decades of gerontological research. The Busse Research Award will be given to investigators who have conducted significant research early in their careers in gerontology. Busse is Gibbons Professor Emeritus and former chairman of the Department of Psychiatry at Duke University Medical Center.

Stanley S. Kahn, M.D. '43M, has received the Laureate Award of the American College of Physicians. He also received the Outstanding Physician Award for 1990 from the medical house staff of BMC Montclair Hospital, where he currently teaches. In August, the Medical

Library at BMC Montclair was named in his honor during a rededication ceremony. Kahn retired from active medical practice in internal medicine and endocrinology in December 1988.

Royal Lee Brown, M.D. '49, has retired. He earned three Ph.D. degrees, taught at the University of Southern California and at the University of California-Los Angeles, wrote 100 medical and scientific papers, authored three books and was president of three national medical societies during his active career. He now lives in Salt Lake City.

'50s and '60s

Fred T. Caldwell Jr., M.D. '50, has been elected president of the American Burn Association and is serving a one-year term. The American Burn Association has more than 3,000 mem-

bers nationwide. Caldwell has been a member for nearly 25 years.

John D. Davidson, M.D. '52, was recently invited to the Karolinska Institute, Stockholm, Sweden to conduct seminars on the Clinical Management of Carbon Monoxide Poisoning and on the Effect of Hyperbaric Oxygen in Chronic Non-Healing Wounds. Davidson is a cardiologist on the staffs of Barnes and St. Luke's Hospitals and is the director of the Division of Hyperbaric Medicine at St. Luke's.

Ralph H. Harder, M.D. '57, recently ended 27 years of private family practice to work for America West Airlines Medical Department in Phoenix.

Godofredo Herzog, M.D. '57, is chief of the Department of Obstetrics/Gynecology at Christian Hospitals in St. Louis. He has three grandchildren. He recently left a group practice and has

established himself in solo practice.

Ronald G. Evens, M.D. '64, has been elected a director of International Minerals and Chemical Corporation. IMC is the parent company of Mallinckrodt, Inc. Evens is Elizabeth E. Mallinckrodt Professor, head of the Department of Radiology and director of the Mallinckrodt Institute of Radiology.

'70s and '80s

Joseph N. Marcus, M.D. '75, has a new daughter, Ann Margaret Marcus.

Charles O. Hershey, M.D. '77, has been promoted to associate professor of medicine with tenure at the University of Buffalo (State University of New York). He is chief of the Division of General Internal Medicine at the Erie County Medical Center. He and his wife, **Linda A. Hershey, M.D.** '75, keep busy with their children Eddy, Billy and Erin.

Carol Mitchell Simmons, M.D. '79, clinical attending and staff physician at Jewish Hospital, has become a Certified Personal Trainer through the International Dance Exercise Association.

Tom Leung, M.D. '84, is joining private practice in cardiology in Gilroy, California.

Robert Mittl, M.D. '85, and his wife, Valerie, announce the birth of their son, Gregory Stephen. They live in a Philadelphia suburb. Robert is chief resident in radiology at the Hospital of the University of Pennsylvania.



M E D I C A L A L U M N I

CLASSES OF '36, '41, '46, '51, '56, '61, '66, '71, '76, '81

Reunion 1991

Mark your calendars!
May 2, 3, 4

Further information will follow.

Washington University Medical Center Alumni Association
Campus Box 8049
660 S. Euclid Avenue
St. Louis, Missouri 63110
(314) 362-8278

Glen A. Reznikoff, M.D. '89, took time off from his residency in internal medicine at Parkland Hospital to scuba dive around the reefs of Cozumel, Mexico in September.

O T H E R

Margaret Elaine Olson Buss, P.T. '79, and her husband, Robert Q. Buss, sailed around the world from June 1987 until this year. They live in Houston, Texas.

Ley (Shirley) Imboden, O.T. '78, is a fourth-year medical student in Greenville, North Carolina. Prior to medical school, she practiced occupational therapy for eight years in Raleigh, North

Carolina in an infant therapy program and in a pediatric outpatient clinic.

Mary Alice Ryan, H.A.P. '79, was recently appointed president and chief executive officer of St. Andrew's Episcopal-Presbyterian Foundation and its subsidiary, St. Andrew's Management Services, Inc. Ryan served as vice president/COO of St. Andrew's for seven years before her appointment as president.

Donald E. Kilker, M.D. '45, died May 27, 1990.

Arthur T. Esslinger, M.D. '40, died August 20, 1990.

Walter Whitaker, M.D. '27, died August 31, 1990.

John F. Patton, M.D. '28, died November 18, 1990.

IN MEMORIAM

Carroll Behrhorst, M.D. '47, died May 7, 1990.

James F. Nickel, M.D. '48, died May 13, 1990.

William D. Perry, M.D. '47, died May 23, 1990.



Dr. Carl Moore engaged in teaching house officers in the mid-1950s. This is one of several historic photographs that appear in this issue of Outlook to commemorate the School of Medicine Centennial. A special section begins on page 17.

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Ginkgo leaves, like autumn gold, litter the ground outside Jewish Hospital.